Prenatal arsenic exposure and altered protein expression

By Sara Mishamandani

NIEHS-funded scientists reported changes in biological pathways, associated with prenatal inorganic arsenic exposure, in a paper *(http://www.ncbi.nlm.nih.gov/pubmed/24675094)* selected as an Editor's Highlight in the June issue of the journal Toxicological Sciences. The research, led by Rebecca Fry, Ph.D., at the University of North Carolina at Chapel Hill (UNC), is the largest protein-based study of an arsenic pregnancy cohort to date. The work provides insight into the mechanisms linking early life exposure to arsenic with disease susceptibility later in life. It further identifies proteins and pathways that may help in uncovering biomarkers of arsenic exposure and, thus, disease risk.

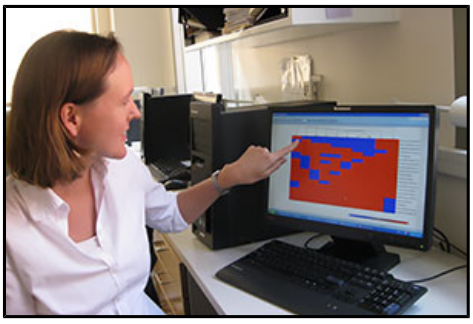
Fry is an NIEHS 2010 Outstanding New Environmental Scientist awardee and a grantee with the UNC Superfund Research Program. She is an associate professor in the UNC Gillings School of Public Health Department of Environmental Sciences and Engineering. (Photo courtesy of Rebecca Fry)

"Health effects associated with exposure to environmental contaminants are determined by the exposure, as well as by how the individual responds to that exposure," said Fry. "This study improves our understanding of the biological mechanisms underlying adverse health outcomes, particularly related to children's health."

Measuring changes in protein levels from arsenic exposure

Fry *(http://sph.unc.edu/profiles/rebecca-fry/)* recently established the Biomarkers of Exposure to ARsenic (BEAR) cohort, a pregnancy cohort consisting of 200 mother-infant pairs residing in Gomez Palacio, in the Lagunera region of northern Mexico, where drinking water contains high levels of arsenic. Fry and her colleagues collected mothers' urine, drinking water, and umbilical cord samples. Using arsenic levels found in the urine and drinking water as a guide, researchers then chose 50 mother-infant pairs, with varying levels of arsenic, for conducting the protein analysis.

Using a large-scale screen of protein levels, researchers identified 111 altered proteins in the cord blood of infants prenatally exposed to arsenic. Almost half of these proteins are regulated by tumor necrosis factor (TNF), which plays a critical role in inflammation, as well as cellular growth and development-related signaling.



Fry uses systems toxicology to understand the molecular mechanisms by which early-life exposures to metals are associated with long-term health effects in humans. (Photo courtesy of UNC Superfund Research Program)

"Using an analytical framework to target biological pathways associated with the altered proteins, we can pinpoint the master regulators of the response to arsenic exposure," said Fry. "The identification of these key players, such as TNF, informs the mechanisms of disease and helps us target novel molecules for arsenic health effects research."

Understanding differences in response to arsenic

Fry and her research team also observed differences in protein expression levels among infants exposed to arsenic. Of the 50 newborns, 30 were considered activators, exhibiting higher than average protein expression levels. The remaining 20, the repressors, displayed lower protein expression levels.

A relationship between increased maternal arsenic levels and decreased head circumference at birth was found in activator males. According to the authors, the relationship between prenatal arsenic exposure and head circumference may be linked to health effects later in life because, in general, there is a positive relationship between head circumference at birth and childhood cognitive ability.

Of potential interest to this study, research based in Torreon, Mexico, a city neighboring Gomez Palacio, demonstrated that boys and girls differed in terms of cognitive deficiencies associated with arsenic exposure, with more cognitive deficiencies observed in boys than girls.

More than 100 million people worldwide are exposed to inorganic arsenic levels exceeding the World Health Organization recommended drinking water limit of 10 micrograms of arsenic per liter. Long-term exposure to arsenic can result in chronic health conditions, such as cardiovascular disease, diabetes, and cancer. Exposure to high levels of arsenic during pregnancy is

also associated with risks to maternal and fetal health, and childhood exposure can bring adverse health effects later in life, including increased rates of lung, bladder, and liver cancers.

The results of this study provide an important foundation for further understanding the relationship between prenatal arsenic exposure, protein response, and disease susceptibility. The identified proteins may also serve as novel targets for understanding arsenic-associated effects on fetal growth and disease later in life.

***Citation*:** Bailey KA, Laine J, Rager JE, Sebastian E, Olshan A, Smeester L, Drobna Z, Styblo M, Rubio-Andrade M, Garcia-Vargas G, Fry RC.
(http://www.ncbi.nlm.nih.gov/pubmed/24675094)
2014. Prenatal Arsenic Exposure and Shifts in the Newborn Proteome: Interindividual Differences in Tumor Necrosis Factor (TNF)-Responsive Signaling. Toxicol Sci 139(2):328-337.

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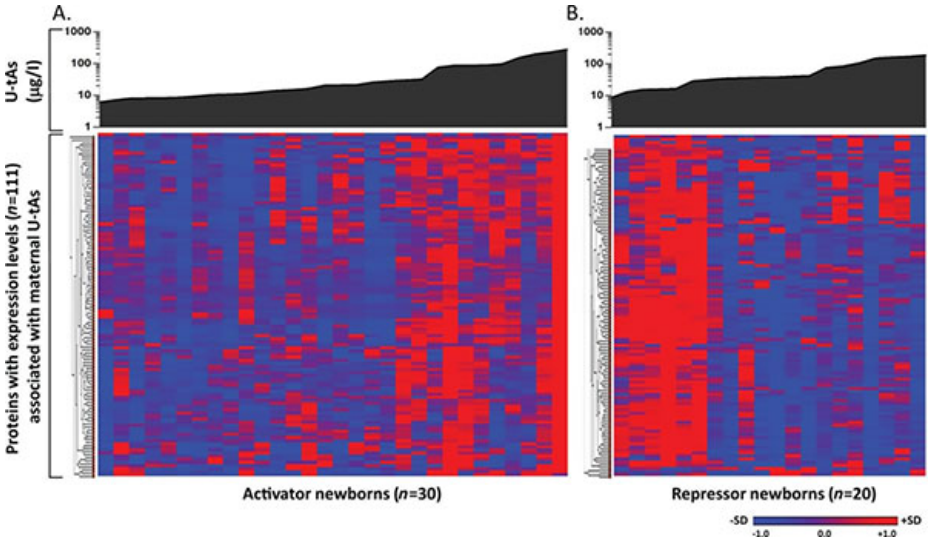

Researchers used heat maps to illustrate the relative expression levels of the 111 proteins associated with arsenic exposure in activator and repressor newborns. High relative expression is indicated in red and low relative expression is indicated in blue. As the level of maternal urinary arsenic (U-tAs) increased, activator newborn protein expression also increased, whereas repressor newborn protein expression decreased. (Image source: Bailey KA, et al. Toxicol Sci 139:328-337)

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